LEAD OPTIMIZATION COMPLETED (1/2)

GLOBAL DRUG DEVELOPMENT

Goals/ Definition

To evaluate basic pharmaceutical properties such as solubility, stability, and physical state of multitude of chemical modifications of the lead scaffold.

Lead optimization completed and candidate for preclinical candidate development selected.

CRITERIA	SAMPLE CONTENT REQUIREMENT	GUIDELINES FOR LEVEL OF DETAIL NEEDED AT EACH GATE
▪ Lead candidate optimized	a) *In vitro*, *in silico* & *in vivo* (animal) model development and dose response relationships established. b) Preliminary *in vitro* / *in vivo* safety / toxicology & *in vivo* efficacy (e.g., safety pharmacology, acute toxicology, genotoxicity, cytotoxicity, reactive metabolite formation) c) PK and ADME properties optimized and modeling indicates likely to achieve TPP PK goals in human. d) PK-PD relationship established using animal model of disease state (preferred) or alternate functional assay e) Biomarker ID in place for target engagement f) Off-target screening in place and selectivity achieved g) Initial pharmaceutical considerations (e.g. stability, solubility, synthetic feasibility, formulation strategy, etc.) h) Preclinical candidate selection justification package	▪ Summary of key data to substantiate conclusions ▪ Illustrative data tables or figures may be reported in an appendix
▪ Drug combination assessment	a) Need for combination considerations b) Assessment strategy	▪ One page summary
▪ Candidate molecule meets target product profile	a) Alignment with Foundation (intervention) target product profile b) Feasibility and benefit over existing treatments	▪ The cTPP and iTPP may be compared side by side in a table format

***Candidate progression is discussed at standing grantee update meetings with the investment team**

LEAD OPTIMIZATION COMPLETED (2/2)

GLOBAL DRUG DEVELOPMENT

Goals/ Definition

To evaluate basic pharmaceutical properties such as solubility, stability, and physical state of multitude of chemical modifications of the lead scaffold.

Initial drug substance characterization completed and preclinical formulation developed.

CRITERIA	SAMPLE CONTENT REQUIREMENT	GUIDELINES FOR LEVEL OF DETAIL NEEDED AT EACH GATE
▪ Initial drug substance characterization completed *** CMC experts should be engaged to assess physicochemical properties**	a) Molecular & physicochemical properties (e.g., chirality /enantiomer inter-conversion, solubility (pKa, Log P/Log D), permeability (Caco-2 permeability coefficient), BCS classification, etc.) b) Thermal analysis, DSC c) Salt & form screening (e.g., amorphous vs. crystalline, polymorph ID, etc.) d) Drug substance / preliminary drug product stability studies (e.g. solid state drug substance stability, metabolic stability) e) Chemical purity (e.g., impurity identification & profiles, analytical methods) f) Stability studies (e.g., T, pH, humidity, light, metabolic stability, etc.) g) Stable, bioavailable salt/form selected	▪ Summary of key data to substantiate conclusions ▪ Illustrative data tables or figures may be reported in an appendix
▪ Preclinical formulation to support animal studies completed	a) Preliminary drug substance formulation (e.g., salt/form analysis, polymorph characterization, delivery method, confirm bioavailability / PK in animal) b) Formulation considerations related to type of animal studies (e.g. Biomarkers / Preclinical PoC, PKDM and tox studies) and route of administration (e.g. oral / IP / IV / SC) c) Drug substance characterization and formulation for active comparators (known compounds, benchmarks etc.) d) GLP analytical methods for formulation stability and release e) Particle size / oral bioavailability, need for milling / micronization	▪ Summary of key data to substantiate conclusions ▪ Illustrative data tables or figures may be reported in an appendix

***Candidate progression is discussed at standing grantee update meetings with the investment team**